

## Editorial

### Surgical management of unruptured cerebral arteriovenous malformations

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This issue of the *Journal of Neurosurgery* includes an excellent paper by Bervini et al. from Professor Morgan's service at Macquarie University in Sydney, Australia.<sup>2</sup> This well-respected group has one of the largest experiences in the world with cerebral arteriovenous malformations (AVMs). In this study, the authors sought to ascertain the natural history of unruptured brain AVMs with regard to risk of rupture as well as the morbidity and mortality associated with resection. The authors retrospectively identified all patients with unruptured brain AVMs who were referred to their institution from a prospectively maintained AVM database consisting of both treated and untreated lesions. Over a 24-year period, a total of 427 patients with unruptured cerebral AVMs were identified. All patients with more than 1 day of follow-up (n = 377) were analyzed for risk of hemorrhage, irrespective of the management plan, from the date of initial consultation or referral to the date of last available follow-up or until the initiation of treatment. Radiologically confirmed hemorrhage unrelated to treatment occurred in 16 patients during a total of 279 case-years of follow-up. Permanent disability following hemorrhage resulted in a modified Rankin Scale (mRS) score > 1 in 88% (14 cases), mRS score > 2 in 69%, and death in 31% of the patients. The cumulative rate of hemorrhage using Kaplan-Meier analysis at 1 and 5 years was 8.1% and 11.5%, respectively. The annualized risk of hemorrhage over the first 5 years was 2.3%. The only variable associated with a significantly shorter time to hemorrhage was deep location by univariate analysis.

The risk from resection was assessed in 2 ways. First, the authors analyzed the surgical outcomes in patients who actually underwent resection based on AVM grade. The authors classified AVMs according to Spetzler-Ponce Class where Class A comprised Spetzler-Martin Grade I and II lesions, Class B comprised Spetzler-Martin Grade III lesions, and Class C comprised Spetzler-Martin Grade IV and V lesions. Complications were defined as any permanent neurological deficits following surgery,

including those related to preoperative embolization, that resulted in an mRS score > 1 at last follow-up. The authors then performed an interesting sensitivity analysis to estimate the true risk of surgery for all AVM grades and not only those selected based on a perceived favorable risk-benefit ratio. The authors included patients who were eligible for surgery but did not undergo resection because of perceived excess surgical morbidity with those who actually underwent resection. Patients were considered eligible for surgery if they were younger than 65 years and did not have significant comorbidities. These added unoperated cases were assumed to have an adverse outcome for the purpose of the sensitivity analysis.

For patients with Spetzler-Ponce Class A lesions treated by surgery (n = 190), the risk of a new permanent deficit resulting in an mRS score > 1 or mRS score > 2 was 1.6% and 0.5%, respectively. None of the eligible patients with Spetzler-Ponce Class A lesions were excluded because of perceived excessive surgical risk and thus a sensitivity analysis was not performed. For patients with Spetzler-Ponce Class B lesions treated by surgery (n = 107), the risk of a new permanent deficit resulting in an mRS score > 1 was 14% and mRS score > 2 was 2.8%. Two eligible patients with Spetzler-Ponce Class B lesions were excluded because of perceived excessive surgical risk. The sensitivity analysis showed that if these cases had been included the risk of a new permanent neurological deficit resulting in an mRS score > 1 or mRS score > 2 would have been as high as 15.6% and 4.6%, respectively. For patients with Spetzler-Ponce Class C lesions treated by surgery (n = 44), the risk of a new permanent deficit resulting in an mRS score > 1 was 38.6% and an mRS score > 2 was 15.9%. Twenty-five eligible patients were denied surgery due to perceived excessive surgical morbidity. The sensitivity analysis showed that if these cases had been included the risk of a new permanent neurological deficit resulting in an mRS score > 1 or mRS score > 2 would have been as high as 60.9% and 46.4%, respectively.

The authors then superimposed the risk of surgery resulting in an mRS score > 1 upon the Kaplan-Meier curve of the risk of hemorrhage and found that the crossover occurred before 5 months for Spetzler-Ponce Class A lesions and between 8 and 9 years for Spetzler-Ponce Class B lesions but did not occur for Spetzler-Ponce Class C lesions. When surgical outcomes resulting in an mRS score > 2 were superimposed, the crossover occurred before 5 months, between 6 and 8 months, and beyond 8 years for Spetzler-Ponce Class A, B, and C lesions, respectively. The authors concluded that surgery for Spetzler-Ponce

Class A unruptured cerebral AVMs beats the natural history. They further confirmed this conclusion by superimposing the most optimistic boundary of the natural history (the upper 95% confidence interval for not experiencing an adverse outcome) with the most pessimistic boundary of the surgical sensitivity analysis (the lower 95% confidence interval for not experiencing an adverse outcome) and found that the crossover occurred within 9 years for mRS score > 2 and within 3 years for mRS > score 1, suggesting a 90% chance of surgical benefit over conservative treatment within 3 years for unruptured Spetzler-Ponce Class A AVMs. On the other hand, a similar analysis for Spetzler-Ponce Class B and Spetzler-Ponce Class C lesions suggested that surgery might not be better than conservative management.

The article, which is very well written and discussed, has some limitations, which were acknowledged by the authors. This was a nonrandomized retrospective analysis of a prospective cohort of patients. The natural history data presented by the authors must be interpreted with some skepticism. They studied patients from the time of diagnosis to the time of treatment, hemorrhage, or the date of the last follow-up in those patients who did not have hemorrhage or treatment. In this group of patients, the average time between initial referral and treatment, hemorrhage, or last follow-up was 270 days with a range of 1 to 5840 days. Why such a delay in treatment in these patients? One could conceive that there was a bias in delaying treatment in those patients who for one reason or another were suspected to have a lesser risk of hemorrhage. Nevertheless, the risk of hemorrhage of approximately 2.3% per year during the first 5 years of follow-up calculated in this fashion by these authors is very similar to that found in other studies that address specifically the natural history of unruptured AVMs, as discussed and referenced by the authors.

More straightforward are the data provided by the authors in their surgical results. Clearly, it could be argued that the results of a highly skilled and extremely experienced neurovascular surgeon such as Professor Morgan cannot be generalized. However, his results are comparable to those reported in several series, including our own.<sup>1,4,6-8</sup> Still, it is very likely that these excellent results can only be achieved in centers with considerable experience in the treatment of AVMs, and, in this respect, the results reported in this study may not be generalizable; however, should not most patients with such relatively uncommon and complicated lesions as cerebral AVMs be referred for elective treatment to experienced centers?

Undoubtedly, the design of this retrospective study was intended as a direct challenge to the recently reported A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) results. We have commented in some detail in a recent editorial on the need to exert caution in the interpretation of the results of the ARUBA study and we will not repeat that discussion here.<sup>3</sup> The fact is that, despite the widely discussed limitations of the results of the ARUBA studies, many have interpreted such results as indicative of the fact that no unruptured cerebral AVM should be treated at all. Hence, the importance of the study by Professor Morgan and his colleagues that,

when supplemented by similar results reported in other large series, provide robust support for recommending treatment, specifically excision, to all relatively young and healthy patients with an unruptured Spetzler-Martin Grade I or II AVM. The results of treatment, which is frequently multimodality, with Spetzler-Martin Grade IV and V AVMs, even in the best hands, as evidenced in this particular study, strongly argue against recommending treatment to patients with unruptured high-grade AVMs. As many have discussed, including ourselves in a recent editorial,<sup>3,5</sup> decision making with Spetzler-Martin Grade III malformations is indeed difficult since this is a very heterogeneous group of lesions. Suffice to say that with these AVMs, treatment decisions must be highly individualized and that in general, when dealing with unruptured Grade III AVMs, a relatively conservative attitude is desirable.

We thank Professor Morgan and his group for providing us with an excellent article that, we believe, will be highly influential.

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#### Disclosure

The authors report no conflict of interest.

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## Response

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We thank the authors for their thoughtful response to our article. Two issues raised by the authors that need to

be addressed include delay to treatment and the generalizability of the surgical results.

The delay between referral and treatment was incorporated in the calculation of the natural history data. This was important in our study as we needed to find the 95% confidence intervals of the risk of first hemorrhage for the purpose of our comparison between surgery and no treatment of unruptured brain AVMs (ubAVMs). No 95% confidence interval existed in the literature. Therefore, we included the period between referral and surgery in the operated cases along with the unoperated cases to establish the 95% confidence interval of the risk of next rupture. Because at 5 and 6 years the mean fell into the 95% confidence interval range of means reported in the meta-analysis of Gross and Du,<sup>1</sup> we believe our results for next hemorrhage reflect the experience of others. The delay to treatment average differs considerably from the medians. The median time between referral and treatment was 27 days (75th percentile 60 days), 38 days (75th percentile 94 days), and 67 days (75th percentile 176 days) for Spetzler-Ponce Class A, B, and C lesions, respectively.<sup>2</sup> For ubAVMs this time delay is not unusual, as in our practice we encourage patients to take time to think about what we have recommended before coming to a final decision. This is especially so for the more complex brain AVMs (bAVMs). Of course, this influences the mix of cases in the risk to rupture group (represented by more high-grade bAVMs). Having said this, there is little compelling evidence that suggests that different grades of unruptured bAVMs have different risk of rupture.

The question of generalizability of results is also important. We accept that in cohort studies the results are probably not generalizable. However, as Drs. Elhammady and Heros point out, and as Spetzler and Ponce have re-

viewed, there are a number of surgical series with very similar results to ours (although these series incorporate both ruptured and ubAVMs).<sup>2</sup> We believe that the important question of generalizability is of lesser importance than answering the question asked by ARUBA or by our study. There is a fundamental difference in these questions. ARUBA has asked, “IS” treatment of ubAVMs (by methods commonly recommended in units with a bias towards treatment modalities that are non-surgical) superior to no treatment (“best medical management”)? However, our question was, “CAN” surgical treatment of ubAVMs be superior to no treatment? This is not addressed by ARUBA in which 82% of patients in the treatment arm were treated by means other than surgery. We believe that surgical treatment of ubAVMs can be superior to no treatment and that this conclusion in our study is realistic.

The argument regarding the type of center that should manage bAVMs is important. Centralization in academic or specialized units may have an advantage to ensure that there are enough cases of bAVMs to facilitate expertise in surgical treatment, benchmarking of outcomes, and modification of practice (continuing learning).

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